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| 10/528,304 | 03/17/2005 | Stephen D. Goble | 21030P | 6448 |

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| EXAMINER | |
|---|---|
| O'DELL, DAVID K | |

| ART UNIT | PAPER NUMBER |
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| 1625 | |

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|---|---|
| 08/05/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/528,304 | GOBLE ET AL. | |
| | Examiner | Art Unit | |
| | David K. O'Dell | 1625 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8-12 and 18-24* is/are pending in the application.

4a) Of the above claim(s) *19-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-12,18 and 23* is/are rejected.

7)☒ Claim(s) *8-12,18 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/22/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**1.** This application is a 371 of This application is a 371 of PCT/US03/34002 filed 10/24/2003 which claims priority to U.S. Provisional 60/422,447 filed 10/30/2002.

Claims 8-12, 18-24 are pending. Claims 19-22 are withdrawn.

### *Response to Applicant's Arguments and Remarks*

2. Applicant's arguments submitted April 22, 2008 have been carefully considered yet they do not overcome the 112 1st paragraph rejection of record. The applicant's representative has argued that the claims are enabled by making reference to two commonly assigned copending applications. The document US 2006-0116421 (Butora I) discloses 233 compounds of these only 6 compounds lack the $CF_3$ methyl group (Examples 22-24, 27, 55 & 61). Apparently based on the remarks at page 11, "Note that the compounds in Butora I were chosen because they have an $1C_{50}$ of less than 1 μM in the binding assay, as was the case with the current claims.", the applicant has chosen these six examples because they have $IC_{50}$'s of less than 1 μM. Contrary to the applicant's assertion the examiner finds no $IC_{50}$ data in Butora I, but rather nebulous statements with regard to the activity:

> **[0090]** In particular, the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an $IC_{50}$ of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

Since the compounds of Butora I, generally contain a trifluromethyl group (97.5% of the compounds), the general statements at [0090] are referring to these compounds. However not

withstanding these considerations, the definition of $R^2$ with respect to the phenyl substituents underlined below, is disturbing:

$R^2$ is selected from the group consisting of -$CH_2$-phenyl, -$CH(CH_3)$-phenyl, and -$C(CH_3)_2$-phenyl, wherein phenyl is unsubstituted or substituted with 1-3 substituents independently selected from:

(a) halo,
(b) trifluoromethyl,
(c) trifluoromethoxy,
(d) hydroxy,
(e) $C_{1-3}$alkyl,
(f) -O-$C_{1-3}$alkyl,
(g) -$CO_2$-$C_{1-3}$alkyl,
(h) -$CO_2H$,
(i) -S-$C_{1-3}$alkyl,
(j) -$SO_2$-$C_{1-3}$alkyl,
(k) -$SCF_3$,
(l) -$NH_2$,
(m) -NH-$SO_2$-$C_{1-3}$alkyl, and
(n) -$SO_2$-$NH_2$;

Of course the specification teaches only fluorine and hydroxy as alternative substituents, but even when considering these groups in the context of Butora I, it is unreasonable to believe these groups are active compounds. After carefully reviewing Butora I, it is clear that only hydroxy, halogen, CN, $OCH_2CF_3$, triazole and tetrazole were used in addition to trifluoromethyl. One could argue that tetrazole is an equivalent of the carboxylic acid group claimed (i.e. (h)) but beyond this could one argue that al these groups are obvious variants? Why would one substitute a trifluoromethyl with a sulfonamide? The same can be said for US 2005-0261325 (Butora II), which of 163 compounds teaches only 16 compounds without a trifluoromethyl group (while the applicant's representative has pointed to 18 compounds, of these compounds 18-7, and 35 do not contain a $CF_3$ group). The examiner welcomes the submission of data for Examples 22-24, 27,

55 & 61 of Butora I and the examples of Butora II, which may weigh in favor of the enablement of other groups.

With respect to the Pinkerton reference the examiner takes applicant's representatives point about the nature of the changes to the linker of Pinkerton being drastic. It is debatable as to what the "linker" actually is in the instant case, but the examiner does not take issue with the methylene, or dimethyl substituted methylene joining the phenyl ring to the amido nitrogen. More appropriately, the linker may be viewed as the cyclopentyl joining the benzylamide to the piperidine ring. If this is the case, the specification does not support the diverse array of groups on R1 as the "linker". For R1 the specification only teaches propyl optionally substituted with hydroxy, however the claims are not even remotely commensurate in scope with this teaching, as shown below for R1:

$R^1$ is selected from the group consisting of:

(1) $-CH_3$,
(2) $-CH_2CH_3$,
(3) $-CH(CH_3)_2$,
(4) $-CH_2CH_2CH_3$,
(5) $-CH_2CH(CH_3)_2$,
(6) -cyclopropyl,
(7) -cyclobutyl,
(8) -cyclopentyl,
(9) $-CH_2$-cyclopropyl,
(10) $-CH_2$-cyclobutyl,
(11) $-CH_2$-cyclopentyl,
(12) $-CH_2OH$,
(13) $-C(CH_3)_2(OH)$,
(14) $-C(CH_2OH)(CH_3)_2$,
(15) -(OH)cyclobutyl,
(16) -(OH)cyclopentyl,
(17) $-C(CH_3)_2(NHCOCH_3)$,
(18) $-C(CO_2H)(CH_3)_2$,
(19) $-O-CH_3$,
(20) -O-cyclopentyl,
(21) $-O-CH(CH_3)_2$,
(22) $-S-CH_3$,
(23) $-S-CF_3$,
(24) $-SO_2-CH_3$,
(25) $-S-CH(CH_3)_2$,
(26) $-SO_2-CH(CH_3)_2$, and

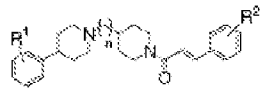
(27) $-NH-SO_2-CH_3$;

The examiner is at a loss to explain how, one of skill in the art arrives at this generic description from the example of propyl and hydroxypropyl, given the Pinkerton teaching against modifying the linker.

The applicant's representative has also taken issue with the examiner's reference to Xia et. al., who showed that modest structural changes led to inactive compounds, and has argued

that ratio of 1:12 inactive to active compounds is not that bad (remarks at 11). A closer examination of the Xia teaching, points to several flaws in this argument: 1) Xia made very modest changes, such as the position of single methoxy on a phenyl ring (compounds **3a**, **3b** & **3c**).

Table 2. Analogs containing a second piperidine ring of structure 3 from Figure 1



| Compound | $R^1$ | n | $R^2$ | CCR2B binding $IC_{50}$ (μM) |
|---|---|---|---|---|
| 3a | 2-Methoxy | 1 | 3,4-Dichloro | 11.1 |
| 3b | 3-Methoxy | 1 | 3,4-Dichloro | 4.0 |
| 3c | 4-Methoxy | 1 | 3,4-Dichloro | 0.32 |
| 3d | 4-Dimethylamino | 1 | 3,4-Dichloro | 0.95 |
| 3e | 4-Hydroxy | 1 | 3,4-Dichloro | 0.51 |
| 3f | 4-Methyl | 1 | 3,4-Dichloro | 2.2 |
| 3g | 4-Chloro | 1 | 3,4-Dichloro | 0.30 |
| 3h | 4-Chloro | 1 | 3,4-Difluoro | 2.0 |
| 3j | 4-Chloro | 1 | 3,4-Dimethoxy | 5.9 |
| 3k | 4-Chloro | 1 | 3-Trifluoromethyl | 1.4 |
| 3l | 4-Chloro | 1 | 4-Bromo | 5.2 |
| 3m | 4-Chloro | 1 | 2-Fluoro-4-bromo | 17% at 25 μM |
| 3n | 4-Chloro | 2 | 3,4-Dichloro | 2.9 |

These types of modifications are generally perceived to be obvious in patent law, yet it is clear the results are quite surprising. The applicant's claims are unarguably drawn to much more drastic prophetic changes. 2) Using the criterion of Pinkerton that compounds over 10μM binding affinity are inactive (which is generally art recognized), it is clear that actually two of the compounds are inactive (**3a** and **3m**) leading to a failure rate of around twenty percent. Again, it should be stressed that these are very minor changes, changes that the examiner would not reject. For example if the applicant has claimed a phenyl substituted with a trifluoromethyl (ambiguously positioned), an enablement rejection would not be issued solely for a working example of 3-$CF_3$, even though it could be argued based upon the unpredictability in the art and the specification showing only 3-$CF_3$ that such changes would not lead to active compounds.

With respect to the variable $R^3$ the amendments are welcome however, they are still

overly broad. In particular the specification shows only the following aromatic heterocycles:

> $R^3$ is a heterocycle, wherein the heterocycle is selected from the group consisting of benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof,
>
> wherein the heterocycle is unsubstituted or substituted with 1-3 substituents independently selected from:

It is well known that molecular structure is correlated with physical properties and in particular in heterocyclic chemistry the change from one ring to another often results in dramatic changes in properties. Pozharskii et. al. *Heterocycles in Life and Society* Wiley, 1997, pgs. 1-6):

> "It is rumored that the Russian scientist Beketov once compared heterocyclic molecules to jewelry rings studded with precious stones. Several carbon atoms thus make up the setting of the molecular ring, while the role of the jewel is played by an atom of another element, a heteroatom. In general, it is the heteroatom which imparts to a heterocycle its distinctive and sometimes striking properties. ..... the heteroaromatic compounds, as the most important group of heterocycles, possess, highly specific features....."

Given the diverse behavior and complete lack of activity for certain groups, such prophetic recitations as those of the instant claims should be evaluated carefully. In terms of the "heterocycle" substituent of $R^3$ of the instant case the specification gives only thirteen examples of actual compounds, all of which are heteroaryls. Based upon the sheer unpredictability in the

art it is readily apparent that one could not make/use this very broad invention without undue experimentation. The specification gives literally no guidance with regard to what the requirements for activity are i.e. which substituents would be preferred. Medicinal chemistry is an experimental science. See *Ex parte Herzog, Hershberg, and Coan*, 115 USPQ 195 (Bd. Pat. App. & Int. 1956) affirming the examiner, and stating "it becomes obvious that the expressions defining the organic acids used.....are inclusive of inoperative materials and go far beyond the adequately disclosed subject matter of the specification." And also *Ex parte DIAMOND,* 123 USPQ 167 (Bd. Pat. App. & Int. 1959) where the examiner was affirmed for a scope of enablement rejection, and the court stated:

"the specification contains 23 specific examples, but it will be noted that they are to the preparation of relatively simple compounds.....This must be regarded as a relatively meagre and nonrepresentative disclosure to support claims which embrace millions of compounds. It should also be observed that appellant is working in a field where little prediction is possible and this Board has on several occasions held that the scope of claims should not be unduly extensive in fields where applicability is highly speculative or not explored and that subject matter which relies upon prediction for its support is unpatentable. Ex parte Middleton, 87 USPQ 57 ; Ex parte Kauck et al., 95 USPQ 197 , Ex parte Rosenkranz et al., Pat. No. 2,715,637. In Minnesota Mining and Mfg. Co. et al. v. Carborundum Co. et al., 155 F.2d 746, 69 USPQ 288 , the court held that 'An inventor cannot disclose a small number of components which will serve as a springboard for claiming an entire class.'"

See also: *Schering Corporation v. Gilbert et al.*, 68 USPQ 84 (2d Cir. 1946)

"Theoretically a multitude of substances not as yet found in nature and not as yet compounded could be synthesized, if skilled organic chemists were given the time and materials with which to work, and actually the formulas for them could be written. There is, however, a practical limit upon synthesis, though the extent of that is not fully known, for some of the new theoretical compounds might be impossible to create, and some would be so unstable that they would disintegrate either at once or in short periods of varying length. Moreover, while analogy is at times useful, organic chemistry is essentially an experimental science and results are often uncertain, unpredictable and unexpected."

And *Nationwide Chemical Corporation, et al. v. Wright, et al.,* 192 USPQ 95 (M.D. Fla. 1976)

"with respect to generic claims to chemical and biological inventions, the scope of the claims is limited to what those skilled in the art could reasonably predict from the inventor's disclosure. This precept recognizes that one skilled in these chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances. Thus, in so-called "chemical" patent law practice, the claims of a patent are limited by the scope of what the disclosure reasonably teaches to one skilled in the art."

*In re Prutton*, 96 USPQ 147 (C.C.P.A. 1952)

"The complete list of organic compositions includes, in generic form, most of the organic compounds found discussed in ordinary textbooks of organic chemistry..... It appears to be appellant's view that a selection of an unsaturated hydrocarbon from the first list and of a sulphide of phosphorus from the second list will provide support for the claims here under discussion. The Examiner holds, and properly we think, that the presentation of such lists from which reagents may be selected is not a sufficient disclosure to support claims to a particular class of reaction product which might be produced by proper selection of reagents and determining the conditions of reaction."

*In re Walker,* 22 USPQ (C.C.P.A. 1934)

"It is true, as argued by counsel, that appellant is entitled to claim not only the substance enumerated by him in his specification, but also their equivalents. However, in cases of this character, involving chemicals and chemical compounds, many of which of course differ radically in their properties, it must appear in the specification, either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that "the chemicals or chemical combinations included therein were generally capable of accomplishing the desired result." See *In re Ellis*, 37 App. D. C. 203; *In re Dosselman*, 37 App. D. C. 211; *In re Langmuir*, 20 C. C. P. A. (Patents) 733, 62 F. (2d) 93."

*In Re Sus and Schaefer* 134 USPQ 1962 301-310 (*affirmed*):

"It is, however, consistent with this public purpose embodied in the pertinent statutory requirement that the *invention claimed* shall be no broader than the *invention set forth* in the written description forming a part of the specification……thus it seems to us that one killed in this art would not be taught by written description of the invention in the specification that any 'aryl or substituted aryl radical' would be suitable for the purposes of the invention but rather that only *certain aryl radicals* and certain specifically substituted aryl radicals would be suitable for such purposes." Emphasis in Original.

The examiner has made his case for the enablement rejection and the rejection may be obviated by narrowing the claims and or providing supporting evidence. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 8-12, 18, 23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain compounds it does not reasonably provide enablement for the scope of compounds bearing the extensive list of substituents.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

***(A) The breadth of the claims;***
***(B) The nature of the invention;***
***(C) The state of the prior art;***
***(D) The level of one of ordinary skill;***
***(E) The level of predictability in the art;***
***(F) The amount of direction provided by the inventor;***
***(G) The existence of working examples; and***
**(H) The quantity of experimentation needed to make or use the invention**

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

**(A) The breadth of the claims:** The claims are very broad encompassing all heterocycles, carbocycles and other groups bearing multiple substitutions of unascertainable structure. **(B) The nature of the invention:** This is a chemical invention requiring the synthesis of compounds and such compounds should have activity at CCR2 receptor. **(D) The level of one of ordinary skill**: One of ordinary skill is a practicing organic/medicinal chemist. **(C) The state of the prior art: (E) The level of predictability in the art: (F) The amount of direction**

**provided by the inventor, (G) The existence of working examples, and (H) The quantity of experimentation needed to make or use the invention:** Each one of the factors (**C**, **E-H**) will be discussed in light of the scientific literature when such a factor is being directly pointed to a large capital letter referring to the aforementioned Wands factor will be placed directly after such a remark or explication. The examiner will first consider the Markush structure I.

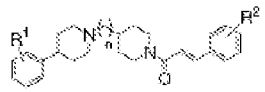
While chemical limitations are important more significant are the limitations of activity at CCR2. What are the important structural features for the claimed utility? It is clear from the data in the specification that the structural features of the compound are of paramount importance for activity. Could the applicant please clarify on the record whether or not the structure is important for the claimed utility. The only information in the specification as to what the molecular determinants are for activity at CCR2 receptor is reproduced here:

> In particular, the compounds of the following examples had activity in binding to the CCR-2 receptor in the aforementioned assays, generally with an $IC_{50}$ of less than about 1 μM. Such a result is indicative of the intrinsic activity of the compounds in use as modulators of chemokine receptor activity.

What does "generally with an $IC_{50}$ of less than about 1μM" mean? In what cases does this generalization not hold true? While the paucity of compounds in the specification (only 64), and no data make a complete evaluation impossible, all the compounds have at least one trifluoromethyl group on the benzyl group and no substituents other than H, F or OH. **(H)** The medicinal chemistry of CCR2 is relatively well-developed and many limitations are well known in the art. It is sensitive to structural changes that may be relatively minor in the chemical sense see Xia et. al. "Synthesis and biological evaluation of phenyl piperidine derivatives as CCR2 antagonists" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 5964-5968, whole document.

In particular compound **3m** is essentially inactive at 25uM and differs from potent antagonists only by the identity and position of a halogen atom.

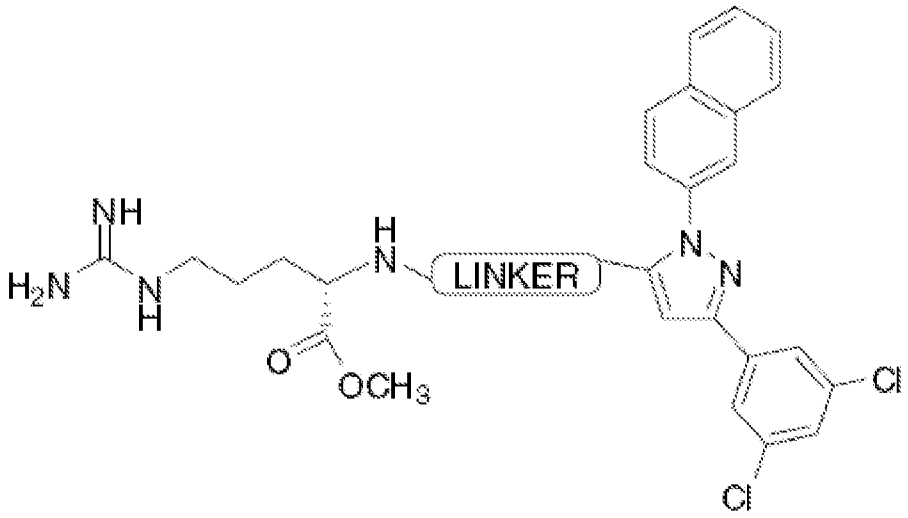
Table 2. Analogs containing a second piperidine ring of structure 3 from Figure 1

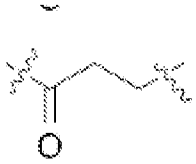
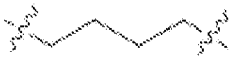
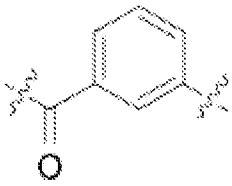
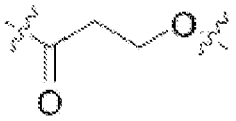


| Compound | $R^1$ | n | $R^2$ | CCR2B binding $IC_{50}$ (μM) |
|---|---|---|---|---|
| 3a | 2-Methoxy | 1 | 3,4-Dichloro | 11.1 |
| 3b | 3-Methoxy | 1 | 3,4-Dichloro | 4.0 |
| 3c | 4-Methoxy | 1 | 3,4-Dichloro | 6.32 |
| 3d | 4-Dimethylamino | 1 | 3,4-Dichloro | 9.95 |
| 3e | 4-Hydroxy | 1 | 3,4-Dichloro | 6.51 |
| 3f | 4-Methyl | 1 | 3,4-Dichloro | 2.2 |
| 3g | 4-Chloro | 1 | 3,4-Dichloro | 0.39 |
| 3h | 4-Chloro | 1 | 3,4-Difluoro | 2.0 |
| 3j | 4-Chloro | 1 | 3,4-Dimethoxy | 5.9 |
| 3k | 4-Chloro | 1 | 3-Trifluoromethyl | 1.4 |
| 3l | 4-Chloro | 1 | 4-Bromo | 5.2 |
| 3m | 4-Chloro | 1 | 2-Fluoro-4-bromo | 17% at 25 μM |
| 3n | 4-Chloro | 2 | 3,4-Dichloro | 2.9 |

In Anthony B. Pinkerton "Diaryl substituted pyrazoles as potent CCR2 receptor antagonists" *Bioorganic & Medicinal Chemistry Letters* **2007**, *17*, 807–813, a study of structure activity relationships reveals the unpredictable and sensitive nature of CCR2 ligands to the structure of the compound:

**Table 2.** Linker modifications




| Compound | LINKER | CCR2 $IC_{50}$ (nM)[a] | Chemotaxis $IC_{50}$ (nM) |
|---|---|---|---|
| 30 |  | 4741 | NT[c] |
| 31 |  | NA[b] | NT[c] |
| 32 |  | NA[b] | NT[c] |
| 33 |  | 62 | 118 |

[b] NA denotes not active <10 μM concentration.

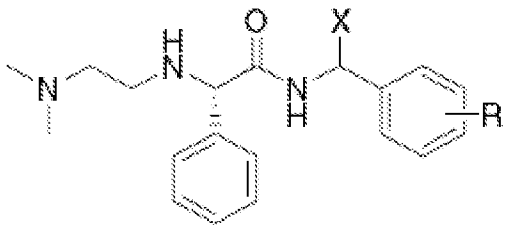
Replacement of an ethyl group in **30** for a phenyl in **32** gave inactive compounds. Where the author stated, "It appears that the SAR is relatively tight for modifications in this area. For example, shortening the chain one carbon, as in **30**, leads to a precipitous drop in activity to 4741 nM. Analog **31** highlights the importance of the central amide for potency—removal of the carbonyl gives a compound that is inactive. Likewise, constraining the linker as in phenyl analog **32** gives an inactive compound."

Perhaps more tellingly are compounds developed by Yang et. al. which are remarkably similar to those of the instant case, Yang et. al. "Discovery of 3,5-bis(trifluoromethyl)benzyl L-arylglycinamide based potent CCR2 antagonists" *Bioorganic & Medicinal Chemistry Letters* **2006**, *16*, 3735–3739. An SAR of the benzylic amide moiety, revealed severe restraints upon the identity of the substituents,

"The **bis-trifluoromethylbenzyl group is extremely sensitive to modification (Table 2). Both of the CF3 groups are critical for activity. Attempts to replace the bis-trifluoromethylbenzyl group with other substituted benzyl groups resulted in inactive compounds (24–27)** as shown in Table 2. The introduction of a methyl at the benzylic position is a way of restricting the number of low-energy conformations at this region, potentially favoring a more active conformation. Unfortunately, in this instance it greatly reduced the binding of compound 28 as compared with the parent 13."

Table 2 is reproduced below for convenience:

Table 2. Binding affinity to human CCR2 (CHO).



| Compound | X | R | Binding $IC_{50}$ (nM) |
|---|---|---|---|
| 24 | H | 2-$CF_3$ | 1% |
| 25 | H | 3-$CF_3$ | 5% |
| 26 | H | 4-$CF_3$ | 7% |
| 27 | H | 3,5-DiMe | 0% |
| 28 | Me | 3,5-Di$CF_3$ | 28% |
| 13 | H | 3,5-Di$CF_3$ | 1000 |

% inhibition at 1 μM when no $IC_{50}$'s were measured.

We have been given no information in regard to the molecular determinants of receptor affinity for the compounds of the instant case, however at least for the $CF_3$ benzyl group the identity cannot be changed and maintain activity. **(F & G)** In this case these compounds bear a structural resemblance to one another, yet the claims are not commensurate in scope. The factors outlined in *In Re Wands* mentioned above apply here, and in particular As per the MPEP 2164.01 (a): "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." It is very clear that one could not make/use this very broad invention that has only

64 examples (that may or may not have activity at CCR2) in this unpredictable art without undue experimentation. **(C, E, F, G, H).**

**Objections**

Claim 24 is objected to for depending from a rejected base claim.

Claims 8-12, and 18 are objected for depending from a later numbered claim.

***Conclusion***

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell whose telephone number is (571)272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571)272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

/Rita J. Desai/
Primary Examiner, Art Unit 1625

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